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Predictive Factors for Complete Removal in Soft Tissue Sarcomas: A Retrospective Analysis in a Series of 592 Cases

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Background and Objectives: In order to specify the indications for conservative surgery and preoperative therapeutic approaches of soft tissues sarcomas (STS), we looked for the clinico-pathological parameters associated with the failure to obtain a complete removal (CRm) of the tumor.
Methods: We retrospectively analyzed a series of 592 cases of primary non-metastatic STS. Surgery was performed in 495 cases as a primary treatment and in 88 cases after chemo- or radiotherapy. Nine patients were treated by chemotherapy-radiotherapy. In a univariate analysis, 20 parameters were tested for their association with CRm. A multivariate analysis was then used to define the independent parameters linked to the achievement of a CRm.
Results: In the univariate analysis, 15 parameters were found to be linked to the achievement of a CRm. Three of them proved to be independent in the multivariate analysis: T in the TNM classification, tumor location, and tumor necrosis. By the combination of these risk factors, four groups of patients were defined, with respective rates of CRm of 97% (no factor), 95% (one factor), 70% (two factors), and 48% (three factors).
Conclusions: The achievement of a CRm after surgery of STS depends not only on the accessibility of the lesion, but also on tumor aggressiveness, a reflection of which is necrosis. The detection of necrosis by imaging procedures may thus help predicting the resectability of tumors and defining the indications for neoadjuvant therapies, likely to broaden the use of conservative surgery.
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KEY WORDS: predictive parameters; neoadjuvant therapy; conservative surgery; tumor necrosis

INTRODUCTION

A variety of approaches in the treatment of primary soft tissue sarcomas (STS) have been proposed. In localized primary tumors, the current trend is toward the use

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of multimodal therapy, including conservative surgery and postoperative adjuvant radiotherapy [1–4], although exclusive radiotherapy may be an alternative in some cases [1].

Achieving complete remission at the end of the primary treatment constitutes a crucial step in the curing of soft tissue sarcomas, and complete surgical removal (CRm) of the tumor is a major factor in ensuring both local control [3] and a satisfactory overall prognosis [5]. The type of surgery performed should disable the patient as little as possible. However, the indications for conservative surgery may be difficult to define: seeking to avoid unnecessary functional suppression, the surgeon runs the risk of performing incomplete tumor removal. Furthermore, the role of neoadjuvant preoperative therapy is still controversial in the management of STS. The initiation of treatment by radiotherapy [6] or chemotherapy [7,8] has been reported to reduce the indications for amputation in initially inoperable extremity STS. However, given the frequency of complications linked to these therapies, it is imperative accurately to identify those patients who are most likely to benefit from them [9].

Therefore, it is important to identify clinicopathological parameters suggesting the small likelihood of obtaining a CRm using the classical sequential therapy. An improved grasp of these criteria would allow for a more accurate preoperative assessment of the tumor, an enhanced evaluation of the prognosis, and would be of potential use in either indicating neoadjuvant therapy in order to attempt tumor reduction or in defining nonconservative surgery.

The aim of our work is to determine the clinical and pathological parameters associated with the failure to obtain a CRm of the disease at the end of the primary multimodal treatment of STS. Indeed, the risk factors for local recurrence of STS (tumoral size and location, histological grading, quality of surgical margins) have been well documented [3], as have the risk factors for metastatic spread of the disease (histological grading, depth, and size of tumor) [10,11], but little is known concerning the risk factors that may be linked to the difficulty involved in obtaining a CRm at the end of the primary multimodal treatment and which can be determined before surgery.

The present work is based on a retrospective analysis of a data base constituted in the Sarcoma Group of the French Federation of Cancer Centers (FNCLCC) [11]. For this study, we used a univariate analysis and looked first of all for the criteria associated with the failure to reach CRm. In the second step, we constructed a logistic regression model in a forward stepwise procedure to carry out a multivariate analysis of these parameters. This model enabled us both to assess the relative influence of predictive factors on the failure to obtain a CRm and also to define groups of patients most likely to be in CRm after common therapeutic procedures. We looked for the value of these predictive factors in two different groups of patients: those treated by primary surgery and those treated by surgery after radio- or chemotherapy.

MATERIALS AND METHODS

Patients

A total of 694 adult patients with STS admitted to one of the 10 participating cancer centers from January 1, 1980 to December 31, 1989, were entered into the data base. A subgroup of 592 patients presented an isolated primary disease and were admitted for curative treatment. The population analyzed was made up of this subgroup. Surgery was performed on 583 patients, either as the first step of the therapy (495 cases, 84.7%) or following chemotherapy (44 cases, 7.5%) or radiotherapy (44 cases, 7.5%). Nine patients were treated by combination chemo-radiotherapy association. CRm was considered to have been achieved when the resection of the tumor was stated as complete by the surgeon and that no residual gross tumor was detectable by either clinical or paraclinical analysis at the end of the primary surgery or multimodal therapy.

Pathology Review

Histological slides of all tumors were retrospectively reviewed by the panel of FNCLCC Sarcoma Group. Histological typing was based on the classification of Enzinger and Weiss [4]. Tumor grade was evaluated according to the FNCLCC system [12,13] based on the extent of tumor differentiation (well, moderately, or poorly differentiated), the mitotic count (<9 mitoses, 10–19 mitoses or >20 mitoses per 10 high power fields) and the presence of necrosis in the tumoral tissue (no necrosis, <50%, >50% of the tumor mass necrotized). Clinical and therapeutic data were obtained from a retrospective review of medical files. All data were entered into a time-oriented data base (Medlog System).

The following 20 variables were analyzed for their potential predictive value: age at presentation, sex, previous history of malignant neoplasia or of neurofibromatosis (von Recklinghausen's disease), tumor size, tumor site (head and neck, limbs, trunk wall, internal trunk/retroperitoneum), T of the TNM classification [14] (T1: tumor size < 5 cm, T2: tumor size > 5 cm without extension to bone or to neurovascular structures, T3: tumoral extension to bone and/or to neurovascular structures), node status (N), tumor depth (suprafascial or intrafascial), tumor extension with regard to anatomical compartments (intra- or extracompartmental), locoregional involvement (with vessels, bone, muscle or viscera), AJCC-UICC staging [14], macroscopical data on tumor (uni- or multilobulated) and on periphery of tumor (encapsulated or infiltrating pattern), histological type, histological differentiation, mitotic count, tumor necro-

sis, histological grade, and presence of intravascular tumor embolisms.

The link between the qualitative variables and the achievement of a CRm was determined by Chi-square tests (Chi^2) and maximum likelihood statistics when needed. For the quantitative variables, an analysis of variance was used. Variables with a P value inferior to 0.15 were tested in the multivariate analysis.

Multivariate analysis was carried out to assess the relative influence of predictive factors for noncomplete remission, using a logistic regression model in a forward stepwise procedure [15]. Due to missing values in 24 cases, this analysis was performed only on a subgroup of 568 patients (479 treated by primary surgery and 89 by primary chemo- or radiotherapy). The statistical significance score in the final model was 0.05. Variables for which >10 values were missing were recorded. A set of nested binary variables was used to enter categorical variables into the logistic model (T, stage, periphery of tumor, necrosis, and histological grade). The weight of every variable was expressed by an odds ratio (OR) corresponding to a risk factor of noncomplete remission.

RESULTS

Characteristics of Patients and Tumors

The population analyzed is composed of 592 patients with primary STS, without overt metastatic disease at the time of the diagnosis, and admitted for curative treatment. The different clinical and pathological data are summarized in Table I.

Complete remission at the end of the primary treatment was achieved in 542 of the 583 patients treated by surgery (93%), and 274 patients were free of disease after a mean follow-up of 59 months (extreme values 4 and 142 months). In 268 patients, a recurrence was observed, at the locoregional area of the primary site in 77 cases, in metastatic location in 111 cases, and in both local and metastatic sites in 80 cases. After a 5-year follow-up, 45% of patients were free of disease, 19% were alive with a local and/or a metastatic recurrence, and 36% were dead of disease.

Univariate analysis showed that 15 of the 20 parameters tested correlated with the achievement of a CRm of the tumor with a $P < 0.15$ (Table II) could be selected for the multivariate analysis. Strongest correlations were observed for (1) T of the TNM status ($P < 0.0001$), (2) the locoregional extension ($P < 0.0001$), (3) the tumor stage ($P < 0.001$), (4) the presence of necrosis in the tumoral tissue ($P < 0.001$), (5) the coexistence of a Recklinghausen disease ($P < 0.01$), and (6) the tumor location ($P < 0.01$).

Multivariate analysis showed that three parameters could be correlated ($P < 0.05$) to the achievement of a CRm (Table III): T of the TNM classification (T3 vs. T1 or T2), the tumor site (internal trunk/retroperitoneum vs. all other sites), and the presence of foci of necrosis of the tumoral tissue (presence of necrosis vs. no necrosis). The ORs of these parameters are 3.7, 3.2, and 2.9, respectively. The fact that these ORs are of similar weight makes it possible to define four groups of patients according to the combination of these three variables and to assess separately in the four groups of patients the chances of reaching a CRm (Table IV).

1. The first group is represented by patients with tumor presenting none of the risk factors defined above. These are T1 or T2 tumors, occurring in sites other than the internal trunk or the retroperitoneum and without necrosis of the tumor tissue. This presentation concerned 172 patients in our series, and 166 of them (97%) presented a CRm at the end of the treatment (95% confidence interval [CI]: 95%–99%).

2. The second group is defined by tumors presenting one of the three parameters at risk for a non-CRm. In our study, this group represented 287 patients. 270 of them (94%) were in CRm at the end of the treatment (95% CI: 92–96%).

3. The third group includes patients with a lesion associated with two risk factors. This was observed in 97 patients, and for 79 of them (81%) a CRm was obtained (95% CI: 75–87%).

4. The fourth group is characterized by patients with tumors associated with all three risk factors. This concerned 12 patients, and only 5 of them (42%) presented a CRm after the treatment (95% CI: 24–60%).

The predictive value of the model was further tested on two populations of patients defined according to the primary treatment used: patients treated by primary surgery (479 cases) and those treated by neoadjuvant chemo- or radiotherapy before surgery (89 cases). In the two populations, response rates were found significantly different ($P < 0.0001$) in the four prognostic groups defined above and the rate of complete remission in each of these groups was of similar value in the two populations of patients (Table V).

DISCUSSION

Surgical procedures for STS have improved over the last decade with better locoregional control after conservative surgery [16,17]. To obtain a CRm after surgery represents a crucial step for the cure of STS, but no predictive factors for the achievement of a CRm have been defined as yet. However, the identification of tumors likely to present only a partial remission may help to specify the type of surgery to be performed and the indication of neoadjuvant therapy. The initiation of radiotherapy [6,18] or systemic chemotherapy [8,19–21] before surgery of sarcomas has theoretical advantages: tumor reduction may allow for conservation surgical therapy, or complete removal of tumors, which otherwise would be inoperable; systemic chemotherapy may be ef-

TABLE I. Soft Tissue Sarcoma Study of Characteristics

A. Clinical characteristics

Variables		Mean value	Range
Age (years)		50.4	15–95
Tumor size (cm)	(data missing: 23)	9.3	1–45
		No. of cases	(%)
Sex	male	316	53
	female	276	47
Previous history of neoplasia	yes	44	7
	no	548	93
Neurofibromatosis	yes	10	2
	no	582	98
Location	head and neck	42	7
	limbs	355	60
	trunk wall	117	20
	trunk/retroperitoneum	78	13
Tumor depth	infrafascial	474	80
	suprafascial	116	20
	(data missing: 2)		
Anatomical extension	intracompartmental tumor	119	35
	extracompartmental tumor	225	65
	(data missing: 248)		
Locoregional extension to:			
—vessels	yes	59	10
	no	522	90
	(data missing: 11)		
—bone	yes	38	7
	no	548	93
	(data missing: 6)		
—muscle	yes	363	62
	no	220	38
	(data missing: 9)		
—viscera	yes	31	5
	no	552	95
	(data missing: 10)		
T (TNM)	T1	168	29
	T2	328	56
	T3	87	15
	(data missing: 9)		
Nodes	negative	573	98
	positive	10	2
	(data missing: 9)		
Stage	stage 1	75	13
	stage 2	223	39
	stage 3	200	34
	stage 4	83	14
	(data missing: 11)		

B. Pathological characteristics of tumors

Variables		No. of cases	%
Tumor growth pattern	unifocal	418	87
	plurifocal	62	13
	(data missing: 112)		
Periphery of tumor	encapsulation	146	47
	partial encapsulation	73	24
	infiltrative pattern	89	29
	(data missing: 284)		
Histological type	MFH[a]	175	30
	liposarcoma	71	12
	MPNST[b]	20	3
	others	326	55

Continued

TABLE I. Soft Tissue Sarcoma Study of Characteristics (Continued)

B. Pathological characteristics of tumors (continued)

Variables		No. of cases	%
Differentiation	well differentiated	18	3
	moderately differentiated	245	41
	poorly differentiated	329	56
Mitotic count (×10 HPF[c])	<9	233	39
	10–19	160	27
	>20	199	34
Necrosis (% of tumor)	0	221	37
	1–49%	320	54
	>50%	51	9
Histological grade	grade 1	80	14
	grade 2	266	45
	grade 3	246	41
Intravascular extension	yes	33	9
	no	342	91
	(data missing: 217)		

[a]Malignant fibrous histiocytoma.
[b]Malignant peripheral nerve sheath tumor.
[c]High power field.

fective for distant micrometastases; and finally, response to preoperative therapy may have prognostic significance and could be used to guide postoperative treatments.

Our study shows that three criteria are predictive for the possibility of obtaining a CRm: the T of the TNM status, the tumor location, and the presence of necrosis foci in the tumoral tissue. The combination of these criteria makes it possible to define four groups of patients with chances of obtaining a CRm of the tumor respectively equal to 97%, 94%, 81%, and 42%. Similar values were also found in the subgroups of patients treated either by primary surgery or by neoadjuvant therapy. Since preoperative radio- or chemotherapy was given to patients with large tumors of unfavorable localization and/or important locoregional extension, the rates of CRm observed in this population favor the hypothesis that neoadjuvant approaches may be of some benefit in these cases and is in accordance with the model described.

In this study, the presence of tumor necrosis was assessed by pathological examination of tumors after surgical removal. To be effective, the determination of predictive factors for a CRm must be performed preoperatively. It is worth stressing that the amount of necrosis of tumoral tissue can be assessed by CT scan analysis, or, better, by multiplanar magnetic resonance imaging [22] (Fig. 1a). The enhanced T1 weighted spin echo images obtained after intravenous administration of gadolinium diethylenetriamine-pentaaceticacid (DTPA), in addition to the nonenhanced T1 weighted images, improve the differentiation of soft tissue from necrotic tumoral tissue (Fig. 1b,c). However, the presence of little necrosis may be difficult to visualize by imaging techniques and revealed only by microscopic examination of a surgical biopsy specimen. It is to be kept in mind that focal necrosis may be missed by Tru-cut biopsy or by fine-needle aspiration technique. However, in most cases, all three criteria defined as predictive for the possibility of obtaining a CRm of STS can be assessed preoperatively. The value of these parameters is maintained in the subgroups of patients treated either by primary surgery or by preoperative chemo- or radiotherapy.

Two of the three parameters predictive for the possibility of obtaining a CRm in STS are merely linked to the surgical accessibility of tumor: T as a combination of size and locoregional extension and the location of the lesion. The third parameter, necrosis of the tumor tissue, is not linked to the accessibility of the tumor but rather corresponds to an indirect reflection of the aggressiveness of the disease. It also may be an indicator of chemosensibility. The evaluation of this parameter, in conjunction with data on tumor size and location, would thus make it possible to recognize patients with lesions difficult to remove entirely and/or more likely to respond to radio- or chemotherapy.

Little data are available on the biological factors that determine the occurrence of necrosis in the tumoral tissue. Necrosis is considered to be a diagnostic criteria of malignancy and corresponds to a major parameter in the histoprognostic grading score of STS [12,23]. Microscopic examination of tumors indicates that necrosis is frequently linked to the degree of dedifferentiation of the neoplastic tissue and to the rate of cellular proliferation. However, the role played by different biological factors in the formation of tumor necrosis has been stressed. The tumor necrosis factor (TNF) can induce necrosis of solid tumors and presents cytostatic and cytotoxic activities toward tumor cells in vitro [24]. It also has been shown to play a role in tumor growth and metastasis [25]. Tu-

TABLE II. Soft Tissue Sarcoma Study of Analysis Results*

Variables		No. of cases	% CR	*P* value
Tumor size (cm)	CRm[a]	9.1	522	0.06
	no CRm[a]	11.1	47	
	(data missing: 23)			
Neurofibromatosis	yes	10	60	<0.01
	no	582	92	
Location	head and neck	42	93	<0.01
	limbs	355	92	
	trunk wall	117	97	
	trunk/ retroperitoneum	78	80	
Tumor depth	infrafascial	474	90	0.01
	suprafascial	116	97	
	(data missing: 2)			
Compartment	intracompartmental	119	96	0.01
	extracompartmental	225	87	
	(data missing: 248)			
Loco-regional extension to:				
—vessels	yes	59	78	0.0001
	no	522	93	
	(data missing: 11)			
—bone	yes	38	84	0.13
	no	548	92	
	(data missing: 6)			
—muscle	yes	363	90	0.07
	no	220	94	
	(data missing: 9)			
—viscera	yes	30	83	0.14
	no	552	92	
	(data missing: 10)			
T (TNM)	T1	168	95	<0.0001
	T2	328	93	
	T3	87	79	
	(data missing: 9)			
Stage	stage 1	75	99	<0.001
	stage 2	223	95	
	stage 3	200	90	
	stage 4	83	83	
	(data missing: 11)			
Periphery of tumor	encapsulation	146	94	0.09
	partial encapsulation	73	95	
	infiltrating pattern	89	87	
	(data missing: 284)			
Histology	malignant fibrous histiocytoma	175	94	
	liposarcoma	71	94	<0.05
	MPNST[b]	20	75	
	others	326	91	
Necrosis	0	221	96	0.001
	<50%	320	90	
	>50%	51	78	
Histological grade	grade 1	80	99	0.02
	grade 2	266	92	
	grade 3	24689		

*Results of the univariate analysis defining parameters to be tested in the multivariate analysis (correlation with complete remission with a *P*-value inferior to 0.15).
[a]Complete removal.
[b]Malignant peripheral nerve sheath tumor.

TABLE III. Variables Associated With Complete Removal of Soft Tissue Sarcomas in the Multivariate Analysis ($P < 0.05$)

Variables	Stepwise	Odds ratio	95% CI[a]
T3 vs. T1 or T2	1	3.7	(1.9–7.2)
Trunk/retroperitoneum vs. other sites	2	3.2	(1.6–6.4)
Necrosis vs. no necrosis	3	2.9	(1.3–6.4)

[a]Confidence interval.

TABLE IV. Groups of Patients With Soft Tissue Sarcoma Defined by the Combination of Different Risk Factors and Respective Rates of Complete Removal in Each Group

	No. of risk factors	No. of cases	Complete removal		95% CI[a]
			No	(%)	
Group 1	0	172	166	(97)	95–99%
Group 2	1	287	270	(94)	92–96%
Group 3	2	97	79	(81)	75–87%
Group 4	3	12	5	(42)	24–60%
		568	420	(74)	

[a]Confidence interval.

TABLE V. Rates of Complete Removal in Soft Tissue Sarcomas According to Nature of Primary Therapy

	Primary surgery		Primary radio- or chemotherapy		
	No. of cases	Complete removal no. (%)	No. of cases	Complete removal no. (%)	
Group 1	148	143 (97)	24	23 (96)	
Group 2	245	230 (94)	42	40 (95)	*P*<0.0001
Group 3	78	66 (85)	19	13 (68)	
Group 4	8	4 (50)	4	1 (25)	
	479	443 (92)	89	77 (87)	

mor development is also largely conditioned by a balance between positive and negative regulators of blood vessel growth [26], and defects in the vascular network of a highly proliferative neoplastic tissue may account, at least in part, for the occurrence of necrosis. The identification of the biological factors conditioning tumor growth should yield a better understanding of the mechanisms leading to the necrosis of tumor tissue and provide better predictive factors for the biological behavior of neoplasia.

CONCLUSIONS

Our work shows that the combination of three parameters easy to define during the initial staging of STS is indicative of the possibility of obtaining a CRm of the tumor at the end of the primary multimodal treatment. Along with the size and localization of tumors,

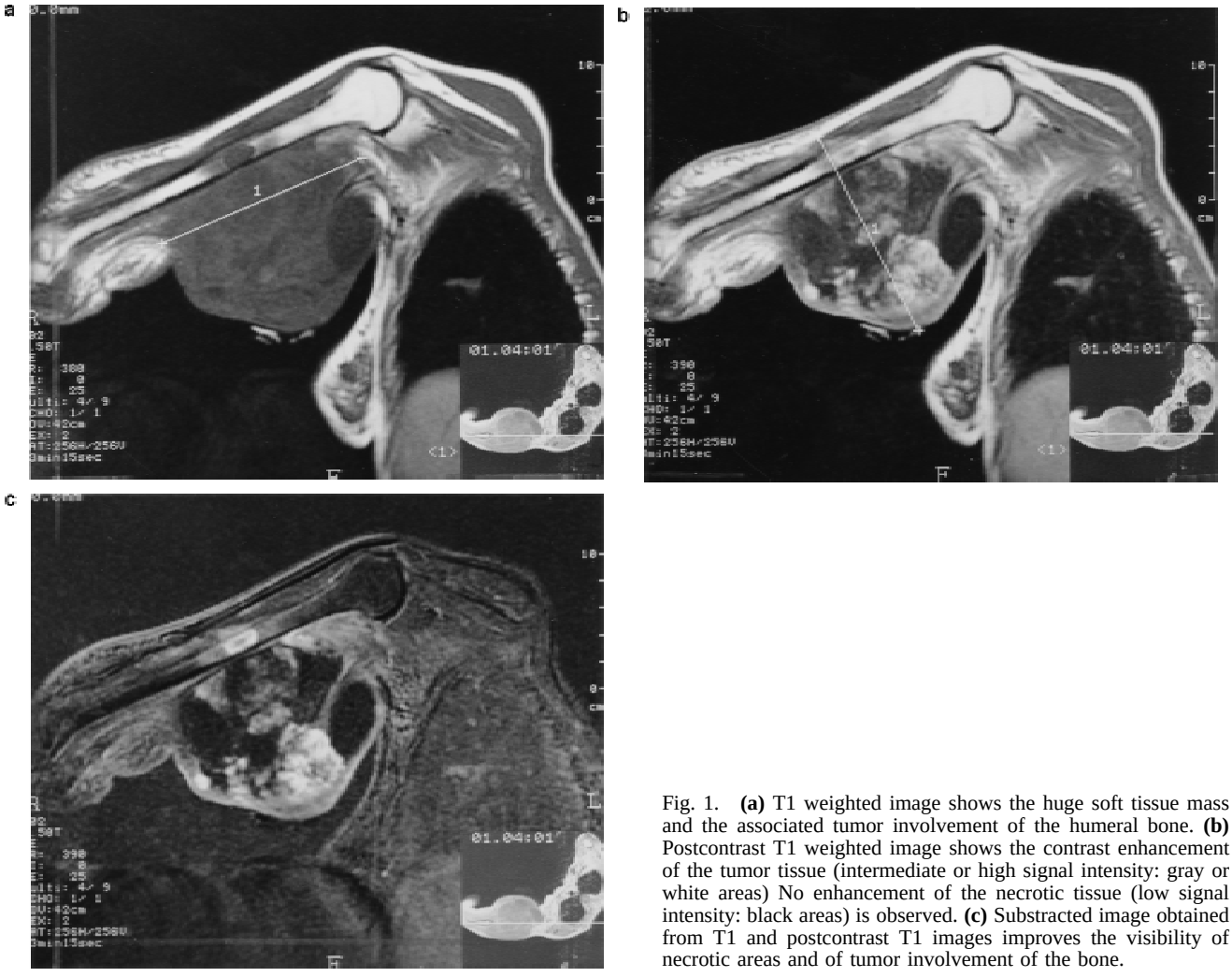

Fig. 1. **(a)** T1 weighted image shows the huge soft tissue mass and the associated tumor involvement of the humeral bone. **(b)** Postcontrast T1 weighted image shows the contrast enhancement of the tumor tissue (intermediate or high signal intensity: gray or white areas) No enhancement of the necrotic tissue (low signal intensity: black areas) is observed. **(c)** Substracted image obtained from T1 and postcontrast T1 images improves the visibility of necrotic areas and of tumor involvement of the bone.

necrosis constitutes a predictive parameter for CRm in adult soft tissue sarcomas and may be taken into account in any assessment of the tumors in order to specify the indications for conservative surgery and those for radio- or chemotherapy as preoperative approaches to STS.

The practical usefulness of this model has to be demonstrated by physicians. An important point is to assess to which extent tumor necrosis may be an indicator of radio- or chemosensitivity, and if neoadjuvant therapy may thus contribute to a significant reduction of the tumor mass in these cases. This should facilitate tumor removal and broaden the indications for conservative surgery. Furthermore, since the complete removal of tumor is very much a function of surgical expertise, the recommendation for sarcomas with two or three poor prognostic factors—particularly of large size and unfavorable location—is that the patients should be referred to centers with large experience with management of these tumors.

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COMMENTARY

This report represents an analysis of a large series of soft tissue sarcomas. The purpose was to identify prognostic parameters that affect the chance for complete removal (CRm) of a soft tissue sarcoma. This information could then be used for patients with a combination of poor prognostic parameters so that preoperative neoadjuvant radiation and/or chemotherapy could be employed, which by reducing the tumor size could increase the CRm rate. Identified poor prognostic parameters are inaccessible location (e.g., retroperitoneum), large tumor size, and tumor necrosis. The first two of these three factors, i.e., location and tumor size, are well known clinically to affect resectability. In a large review study of all published series of retroperitoneal sarcomas up to 1991, it was found that the average resectability rate was 53% and the 5-year survival rate 34% [1]. However, the surgeon's familiarity and experience in removing these tumors are of paramount importance. In our experience, the resectability rate of primary retroperitoneal sarcomas was 100%, those referred with local recurrence 88%, and the overall complete resectability rate was 96%. The 5-year survival rate for these patients was 63% [2]. Given, however, a certain level of surgical expertise available in a community, the identification of the above prognostic indicators by the authors may be helpful in deciding on the advisability of neoadjuvant treatment. However, the efficacy of the latter over the more common approach of resection first, followed by adjuvant treatment as needed (for narrow margins or high grade tumor) only can be definitively assessed in the context of a prospective randomized study.

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